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Effects of Stratification in the Analysis of Affected-Sib-Pair Data: Benefits and Costs

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Summary

The benefits and costs of stratification of affected-sib-pair (ASP) data were examined in three situations: (1) when there is no difference in identity-by-descent (IBD) allele sharing between stratified and unstratified ASP data sets; (2) when there is an increase in IBD allele sharing in one of the stratified groups; and (3) when the data are stratified on the basis of IBD allele-sharing status at one locus, and the stratified ASPs are then analyzed for linkage at a second locus. When there is no difference in IBD sharing between strata, a penalty is always paid for stratifying the data. The loss of power to detect linkage in the stratified ASP data sets is the result of multiple testing and the smaller sample size within individual strata. In the case in which etiologic heterogeneity (i.e., severity of phenotype, age at onset) represents genetic heterogeneity, the power to detect linkage can be increased by stratifying the ASP data. This benefit is obtained when there is sufficient IBD allele sharing and sample sizes. Once linkage has been established for a given locus, data can be stratified on the basis of IBD status at this locus and can be tested for linkage at a second locus. When the relative risk is in the vicinity of 1, the power to detect linkage at the second locus is always greater for the unstratified ASP data set. Even for values of the relative risk that diverge sufficiently from 1, with adequate sample sizes and IBD allele sharing, the benefits of stratifying ASP data are minimal.

Introduction

Nonparametric methods are widely used in the study of complex traits, where mode of inheritance is usually unknown. The advantage of using these methods is that they do not require specification of a penetrance model. Affected sib-pair (ASP) analysis based upon identity-by-descent (IBD) relationships is a popular form of nonparametric linkage analysis. This method has frequently been used to study complex traits including type I diabetes (MIM 222100), type II diabetes (MIM 125853), alcoholism (MIM 103780), bipolar disorder (MIM 125480), and schizophrenia (MIM 181500).

Once a data set has been obtained for analysis, there may be an a priori belief that all families do not share the same genetic disease component. There may be a concern that genetic heterogeneity is present within the data set, because family units have a different disease etiology (i.e., severe or mild phenotypes), different ages of onset (i.e., early and late age at onset), or the families have been ascertained from more than one ethnic population. Examples include the study of migraine with and without aura (Russell et al. 1996) and Alzheimer disease with late and early onset (Pericak-Vance et al. 1991). When analyzing such a data set of ASPs, one may ask the question is it advantageous to analyze the data as a single group regardless of etiologic heterogeneity or to stratify the data on the basis of a predefined criterion?

Another situation arises where there is significant evidence of excess IBD allele sharing found in one or more regions of the genome. In this situation is it beneficial to stratify the data on the basis of IBD sharing status at one locus and test for excess sharing at a second locus? Recently in an ASP study of type I diabetes investigators stratified their data on the basis of IBD status at a first locus (i.e., HLA, insulin) and tested for excess allele sharing at other loci (Cordell et al. 1995; Mein et al. 1998).

This article examines the benefits and costs of stratifying sib-pair data where: 1) there is no difference in IBD allele sharing between the unstratified and stratified groups; 2) there is an increase in IBD allele sharing in one of the stratified groups; and 3) data are stratified based upon IBD status at the first locus and linkage is tested for at a second locus in the two groups.

Methods

The ASP method focuses on pairs of affected siblings and the number of marker alleles shared by the two

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siblings, which are copies of the same parental alleles (IBD). For the ASP method, if sharing is independent of disease status, the expected number of alleles shared IBD is equal to 1; the expected proportion of ASPs sharing zero, one, or two alleles IBD is equal to $\frac{1}{4}$, $\frac{1}{2}$, and $\frac{1}{4}$, respectively. If a given marker is close to a susceptibility locus involved in the etiology of the disease, allele sharing is expected to be increased. The distribution of ASPs over the allele sharing classes zero, one, and two has 2 df and provides information on linkage as well as on mode of inheritance of the disease. Here, interest is only in detecting linkage so it is more beneficial to consider IBD sharing for a given parent rather than for a given sib pair. For one parent, an ASP either does or does not share an allele received from that parent. Each ASP furnishes two such observations. Linkage tests that are based on average IBD sharing tend to be more powerful than those based on goodness of fit to the three allele sharing classes (Blackwelder and Elston 1985).

Generation of Data

For each ASP, alleles shared IBD from each of the parents were examined separately. An ASP could share zero or one allele inherited from the father and zero or one allele inherited from the mother. Each ASP generated is fully informative and there are no ambiguities for the IBD status. For each parent a random number generator was used to determine if a given ASP shares zero or one alleles. The number of alleles shared IBD was summed for a given sample and the corresponding one-sided *P* value was calculated based upon normal approximation.

For each study a total of 20,000 replicates were simulated. The *P* value was calculated for the entire data set of ASPs and for each of the stratified data sets. Because multiple tests were performed for the stratified groups, a Bonferroni correction was used to correct for the multiple testing situation. For the stratified ASP data sets the smallest Bonferroni corrected *P* value was taken as the *P* value for the stratified data sets.

Homogeneity of IBD Allele Sharing

For this situation, there is no difference in the proportion of IBD sharing in the entire data set of ASPs and those ASPs stratified into groups. IBD allele sharing was .52–.7 in the ASP data sets. Data sets with 100, 200, 500, and 1,000 ASPs were analyzed for linkage. They were then divided into two and five strata and reanalyzed.

Heterogeneity of IBD Allele Sharing

Data sets with 100, 200, 500, and 1,000 ASPs were divided into two and five strata. Within the first stratum IBD allele sharing was .52–.7. For the other strata there was no excess of IBD allele sharing (IBD allele sharing equal to .5). Each stratum was tested for linkage and the lowest *P* value recorded. For comparison, the individual strata were reanalyzed as one data set. For this unstratified data set the IBD allele sharing was the weighted average of the IBD allele sharing within the strata.

Stratifying by IBD Status at Locus One and Testing for Linkage at a Second Locus

The ASPs were stratified based upon allele sharing status at a first locus. Those ASPs, which have an allele sharing status of 1 at the first locus, were stratified into one data set and those ASPs with an allele sharing status of 0 were stratified into a second data set. Within each of these data sets, the second locus was tested for linkage. The IBD allele sharing proportions at the first locus had a range of .55–.7 and at the second locus had a range of .55–.7. The power to detect linkage at the second locus was calculated by using a criterion of $\alpha = .0001$ for various values of the relative risk, where IBD allele sharing in each of the stratified groups was $\geqslant .5$. The relative risk is the quotient AD/BC, where A is the number of observations sharing one allele IBD at both locus 1 and locus 2, B is the number of observations sharing one allele IBD at locus 1 and 0 alleles IBD at locus 2, C is the number of observations sharing no alleles IBD at locus 1 and one allele IBD at locus 2, and D is the number of observations sharing no alleles IBD at both locus 1 and locus 2.

Results

Homogeneity of IBD Allele Sharing

When stratification is done on data where there is homogeneity of IBD allele sharing between groups, there is always loss of power to detect linkage. The power decreases as the data are divided into more strata. Figure 1 shows that the power to detect linkage is quite poor for 100 ASPs until the proportion of IBD allele sharing is $\geqslant .63$. For the unstratified data set the power to detect linkage is $>.8$, whereas for the ASPs, which have been divided into five strata, the power equals .45. Table 1 displays the power to detect linkage for the unstratified and stratified ASP data at α levels equal to .01, .001, and .0001 for data sets with 100, 200, 500, and 1,000 ASPs. In no situation did the stratified data perform better than the unstratified data.

Heterogeneity of IBD Allele Sharing

Stratification was done in the presence of heterogeneity of IBD allele sharing between groups, where there was an excess of IBD allele sharing for only one of the stratified groups. In this situation there was an increase in the power to detect linkage, except where the sample

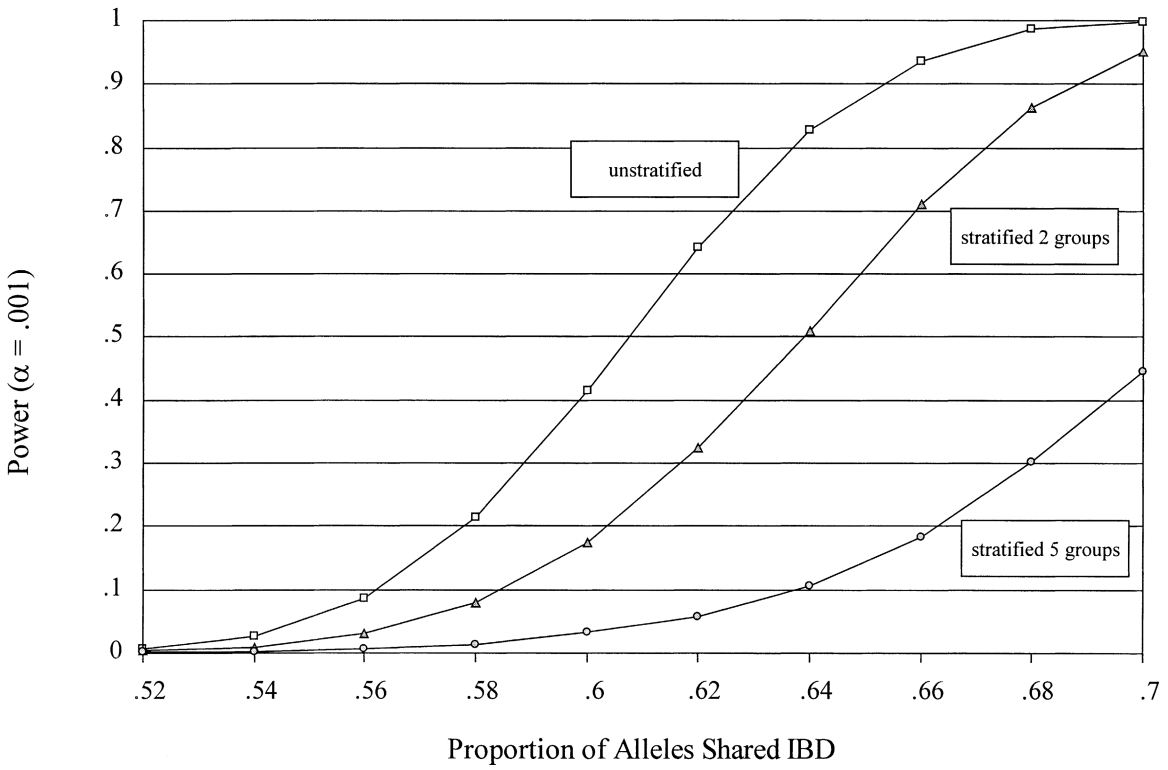

Figure 1 Power to detect linkage at $\alpha = .001$, for 100 ASPs. The ASPs were analyzed both unstratified and stratified into two groups (each with 50 ASPs) and five groups (each with 20 ASPs). The results shown are for IBD allele-sharing proportions of .52–.7.

sizes of ASP data sets were small and the proportion of excess IBD allele sharing was only slightly elevated (e.g., table 2: 100 ASP, 2 strata, $\alpha = .001$, IBD allele sharing equals .54). In the cases were there was a decrease in power to detect linkage in the stratified data sets, the power to detect linkage in both the stratified and unstratified data sets was extremely poor as a result of small sample sizes and low IBD allele sharing.

Table 2 displays the power to detect linkage for α levels equal to .01, .001, and .0001, for data sets of 100, 200, 500, and 1,000 ASPs. The ASPs were analyzed unstratified and stratified in two and five groups. The overall proportion of allele sharing for the unstratified groups is shown in parentheses. For example, where IBD allele sharing in the first stratum is .58 and in the other strata is .5, the overall IBD allele sharing in the unstratified groups is .54 and .516 when the data are divided into two or five strata, respectively.

Figure 2 shows the power to detect linkage for 500 ASPs for various levels of IBD allele sharing. The data were analyzed both stratified (two and five groups) and unstratified. The highest power to detect linkage was obtained for the data set that was stratified into two groups. Where the proportion of alleles shared IBD in the first stratified data set is .6, the power to detect linkage equals .89, whereas for the unstratified ASP data set the power equals .54. The ASP data set that was divided into five strata had less power to detect linkage than both the unstratified and stratified data sets (two groups). This is because of multiple testing and smaller sample size per stratum (100 ASPs compared to 250 ASPs). The unstratified data set where IBD allele sharing equals the weighted average IBD allele sharing of the five stratified data sets has the least power to detect linkage. This is because of the low IBD allele sharing within this data set compared to the other groups.

Stratifying by IBD Status at Locus One and Testing for Linkage at a Second Locus

Data were stratified on the basis of the IBD status at locus 1 and then tested for linkage at the second locus. Figure 3 displays the results for 200 ASPs where the proportion of IBD sharing at the first locus is .6. The power to detect linkage at $\alpha = .0001$ is shown for both the stratified and unstratified data sets where IBD allele sharing at the second locus is equal to .55, .6, and .65. The power to detect linkage at the second locus is graphed for various values of the relative risk in the range 0.6–1.4 (for IBD allele sharing at locus 2 equal to

Table 1

Power to Detect Linkage, for Unstratified and Stratified Analysis of ASP Data

No. of ASPs and Status	Power When Proportion of Alleles Shared IBD Is														
	.52			.56			.60			.64			.68		
	$\alpha = .01$	$\alpha = .001$	$\alpha = .0001$	$\alpha = .01$	$\alpha = .001$	$\alpha = .0001$	$\alpha = .01$	$\alpha = .001$	$\alpha = .0001$	$\alpha = .01$	$\alpha = .001$	$\alpha = .0001$	$\alpha = .01$	$\alpha = .001$	$\alpha = .0001$
100:															
Unstratified	.040	.006	.001	.265	.088	.018	.691	.414	.174	.956	.833	.591	.998	.984	.920
Stratified:															
Two groups	.035	.003	.000	.178	.035	.007	.516	.172	.048	.864	.519	.242	.983	.860	.614
Five groups	.012	.001	.000	.054	.007	.002	.163	.027	.009	.401	.109	.044	.712	.300	.145
200:															
Unstratified	.063	.013	.002	.522	.259	.087	.950	.833	.598	1.000	.996	.972	1.000	1.000	1.000
Stratified:															
Two groups	.041	.006	.001	.327	.098	.025	.827	.514	.254	.994	.936	.780	1.000	.999	.991
Five groups	.034	.004	.000	.185	.037	.004	.560	.192	.034	916	.582	.194	.997	.924	.587
500:															
Unstratified	.148	.037	.008	.934	.767	.537	1.000	1.000	.996	1.000	1.000	1.000	1.000	1.000	1.000
Stratified:															
Two groups	.095	.017	.002	.801	.479	.208	.999	.989	.924	1.000	1.000	1.000	1.000	1.000	1.000
Five groups	.048	.006	.001	.456	.129	.031	.959	.701	.361	1.000	.994	.928	1.000	1.000	1.000
1,000:															
Unstratified	.286	.091	.027	.999	.988	.950	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Stratified:															
Two groups	.183	.040	.009	.987	.898	.714	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Five groups	.096	.015	.002	.858	.477	.178	1.000	.996	.945	1.000	1.000	1.000	1.000	1.000	1.000

Note.—The proportion of IBD allele sharing is equal in both the stratified and unstratified ASP data sets.

Table 2

Power to Detect Linkage, for Unstratified and Stratified Analyses of ASP Data

No. of ASPs, No. of Strata, and Status	Power When Proportion of Alleles Shared IBD Is[a]														
	.54 (.52, .508)			.56 (.53, .512)			.58 (.54, .516)			.66 (.58, .532)			.68 (.59, .536)		
	α = .01	α = .001	α = .0001	α = .01	α = .001	α = .0001	α = .01	α = .001	α = .0001	α = .01	α = .001	α = .0001	α = .01	α = .001	α = .0001
100:															
Two:															
Stratified	.0478	.0058	.0008	.1015	.0174	.0033	.1789	.0424	.0099	.7714	.4596	.2306	.8825	.6277	.3811
Unstratified	.0396	.0064	.0005	.0666	.0143	.0021	.1106	.0263	.0042	.4737	.2134	.0631	.5888	.3054	.1078
Five:															
Stratified	.0097	.0011	.0003	.0158	.0014	.0003	.0231	.0027	.0009	.1535	.0412	.0166	.2224	.0666	.0308
Unstratified	.0174	.0022	.0003	.0227	.0025	.0002	.0289	.0041	.0003	.0757	.0154	.0015	.0903	.0197	.0029
200:															
Two:															
Stratified	.0711	.0132	.0023	.1815	.0507	.0129	.3633	.1417	.0488	.9767	.8975	.7528	.9959	.9694	.8995
Unstratified	.0591	.0118	.0016	.1264	.0334	.0052	.2245	.0720	.0148	.8122	.5619	.2860	.9035	.7196	.4411
Five:															
Stratified	.0267	.0032	.0003	.0514	..0084	.0011	.0882	.0192	.0027	.5407	.2668	.0889	.6813	.4038	.1612
Unstratified	.0213	.0033	.0002	.0313	.0053	.0006	.0438	.0078	.0010	.1371	.0361	.0060	.1751	.0495	.0090
500:															
Two:															
Stratified	.2253	.0699	.0170	.5562	.2808	.1123	.8539	.6316	.3818	1.0000	1.0000	.9995	1.0000	1.0000	1.0000
Unstratified	.1484	.0341	.0068	.3428	.1209	.0357	.5926	.2971	.1195	.9977	.9794	.9165	.9997	.9960	.9792
Five:															
Stratified	.0457	.0069	.0010	.1210	.0282	.0065	.2638	.0866	.0257	.9565	.8357	.6462	.9898	.9428	.8399
Unstratified	.0356	.0047	.0005	.0583	.0110	.0015	.0944	.0192	.0039	.3848	.1441	.0475	.4857	.2109	.0752
Two:															
Stratified	.4887	.2168	.0885	.8925	.6818	.4642	.9938	.9611	.8836	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Unstratified	.2902	.0935	.0259	.6308	.3355	.1470	.8933	.6838	.4413	1.0000	1.0000	.9999	1.0000	1.0000	1.0000
Five:															
Stratified	.1079	.0239	.0047	.3332	.1242	.0391	.6403	.3596	.1692	.9999	.9985	.9900	1.0000	1.0000	.9996
Unstratified	.0504	.0081	.0013	.1028	.0223	.0041	.1785	.0462	.0113	.7038	.4047	.1858	.8101	.5417	.3007

[a] Data shown are for the situation in which IBD allele sharing is .54, .56, .58, .66, and .68 in the first stratum and is .5 in the other stratum/strata; data in parentheses are for unstratified groups and are the weighted average of the IBD allele sharing for two and five strata, respectively.

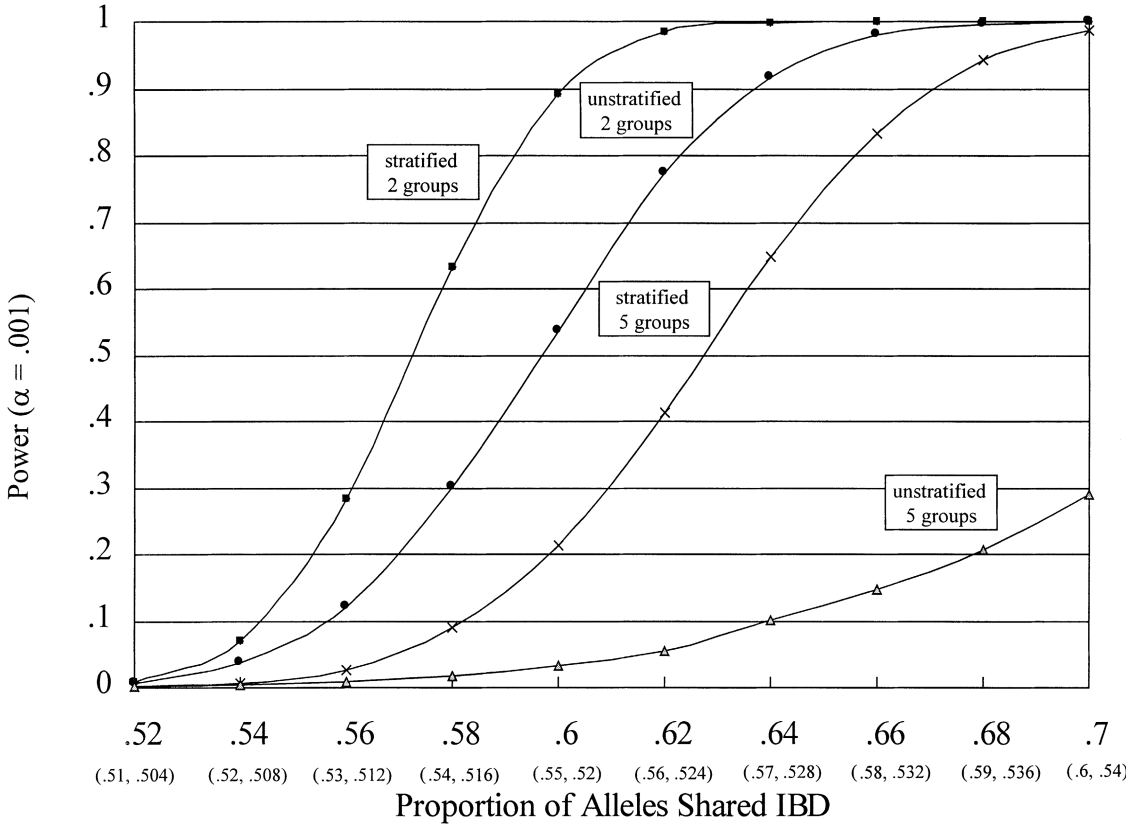

Figure 2 Power to detect linkage at $\alpha = .001$, for 500 ASPs. The ASPs were analyzed unstratified and divided into two strata (each with 250 ASPs) and five strata (each with 100 ASPs). The proportion of IBD allele sharing in the first stratified ASP data set is displayed on the *X*-axis, and the proportion of IBD allele sharing in the other strata is .5. The proportions of IBD allele sharing for the unstratified groups are shown in parentheses; they are the weighted average of the IBD allele sharing for the two strata and the five strata, respectively.

.55), 0.33–2.0 (for IBD allele sharing at locus 2 equal to .60), and 0.14–3.0 (for IBD allele sharing at locus 2 equal to .65). The amount of IBD allele sharing in each of the strata is always $\geq .5$, for those values of the relative risk where this condition was not met the power was not calculated.

For the unstratified ASP data set, the slight difference in power to detect linkage for a given value of IBD allele sharing at locus 2 is due to random variation. For values of the relative risk in the vicinity of 1, there is a loss of power to detect linkage when the data are stratified. The greater the amount of IBD allele sharing at locus 2, the more the relative risk must deviate from 1 for there to be a benefit obtained from data stratification. Where IBD allele sharing at locus 2 is .55 and the data are stratified, there is a loss of power to detect linkage for values of the relative risk that are 0.8–1.2. For IBD allele sharing at locus 2 equal to .6 or .65, there is a loss of power to detect linkage for the stratified ASP data for values of the relative risk that are 0.64–1.41 and 0.51–1.72, respectively. Where IBD allele sharing at locus 2 is equal to .65 and there is an increase in power to detect linkage for the stratified data, the increase in power is small (.99–1.0) (see fig. 3).

Varying the amount of allele sharing at locus 1 from .55 to .65 only slightly changes the results. For example, for IBD allele sharing at locus 1 equal to .55, there was a decrease in power to detect linkage at locus 2 (IBD allele sharing at locus 2 is equal to .65) for the stratified data sets as compared to the unstratified data set, where the relative risk was 0.56–1.63. When the IBD allele sharing at locus 1 was increased to .65, there was only a slight change in the relative risk (0.47–1.60), where there was a loss of power to detect linkage at the second locus for the stratified data set.

The power to detect linkage for various values of the relative risk is plotted in figure 4, where IBD allele sharing at locus 1 is .60 and that at locus 2 is .55, .6, .65, and .7. Here the analysis was carried out with a smaller sample size (100 ASPs). There is a reduction in the power to detect linkage for both the stratified and unstratified data sets. For IBD allele sharing at locus 2 equal to .6 and .65 for relative-risk values of 0.62–1.42 and 0.52–1.72, respectively, there is a decrease in power to

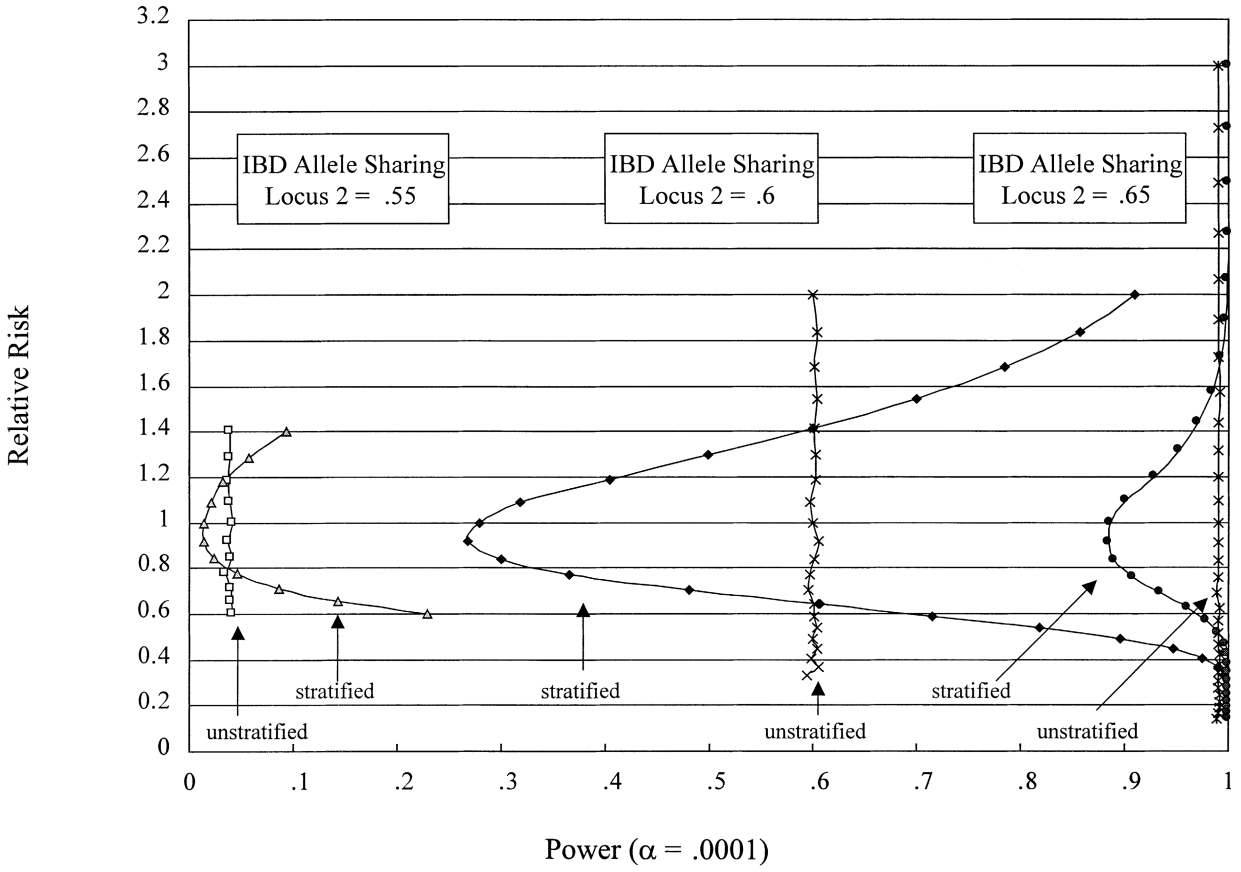

Figure 3 Power to detect linkage at $\alpha = .0001$, for 200 ASPs. The ASPs were analyzed for linkage at locus 2, where the proportion of IBD allele sharing is .55, .6, and .65. The ASPs were then reanalyzed on the basis of their allele-sharing status at locus 1, where the proportion of IBD allele sharing is .6.

detect linkage when the data are stratified. The values of the relative risk where there is a decrease in power to detect linkage for the stratified data set are very similar to the ones observed for the data set with 200 ASPs. Where IBD allele sharing at the second locus equals .7, there is an increase in power to detect linkage in the stratified data set when the relative risk is >2.0 or <0.4. Even when these criteria are met, the increase in the power to detect linkage is modest for the stratified data. The amount that the relative risk must diverge from 1 for there to be a benefit to stratifying the data is dependent mainly on the amount of IBD allele sharing at the second locus.

Discussion

When sib-pair data are stratified where there is no difference in IBD allele sharing between groups, a penalty is always paid for stratifying the data. This is because of the correction made for multiple testing and smaller sample sizes within individual strata. Naturally, with sufficient IBD allele sharing and sample size, significant results will be obtained whether or not the data are stratified.

In the case where there is genetic heterogeneity, stratification can lead to an increase in power to detect linkage with sufficient IBD allele sharing and sample sizes. However erroneously stratifying the data into more groups than necessary will decrease the power to detect linkage. For example, where IBD allele sharing equals .64 in one of the groups and .5 in all other groups, for 500 ASPs stratified into five groups (100 ASPs in each group), the power to detect linkage is .65 for $\alpha = .001$. For 200 ASPs divided into two groups (100 ASPs in each group), the power to detect linkage increased to .74 (table 2). Here the sample sizes are the same in each group, but a penalty has been paid for performing five tests instead of two. If etiologic heterogeneity is the result of genetic heterogeneity, in most cases stratification can increase the power to detect linkage. In cases where power is decreased by stratification, there is very low power to detect linkage in both the stratified and un-

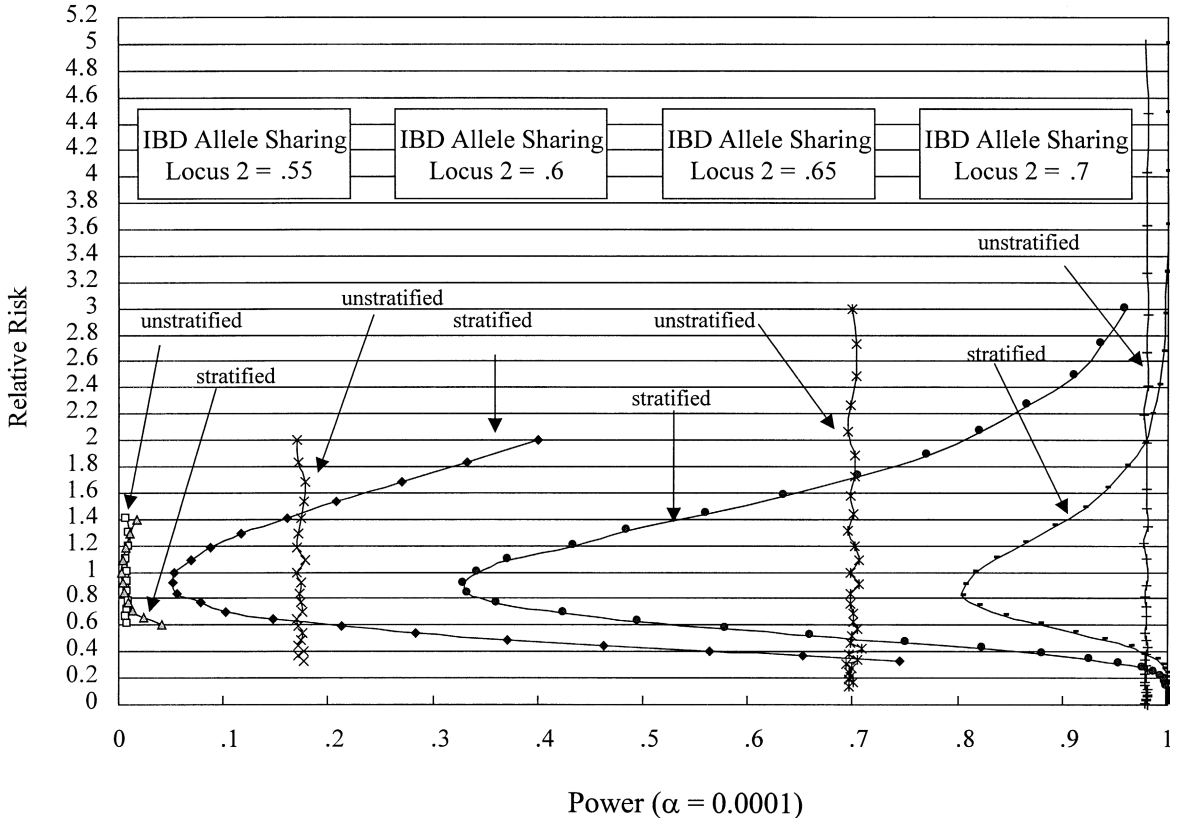

Figure 4 Power to detect linkage at $\alpha = .0001$, for 100 ASPs. The ASPs were analyzed for linkage at locus 2, where the proportion of IBD allele sharing is .55, .6, .65, and .7. The ASPs were then reanalyzed on the basis of their allele-sharing status at locus 1, where the proportion of IBD allele sharing is .6.

stratified data sets. This is due to small sample sizes and a low amount of excess IBD allele sharing.

When data are stratified on the basis of IBD status at one locus and analyzed for linkage at a second locus, with sufficient IBD allele sharing at the second locus and sample size, there is little advantage to stratifying ASP data. The only situation where it is advantageous to stratify these data is when the amount of excess IBD allele sharing at locus 2 and the sample size are small. In this situation additional power to detect linkage can be obtained if the relative risk diverges sufficiently from 1.

The relative risk measures the difference in IBD allele sharing between the two strata. Where the relative risk is equal to 1, the IBD allele sharing in each of the strata is equal to the proportion of alleles shared IBD at locus 2 in the unstratified data set. In this situation the power to detect linkage is lower where the data are stratified due to smaller sample sizes within the strata and multiple testing. As the relative risk diverges from 1, there is an increase in IBD allele sharing in one of the stratum and a decrease in IBD allele sharing in the other stratum compared to the IBD allele sharing at locus 2 in the unstratified data set. The amount the relative risk must diverge from 1 for there to be an increase in power to detect linkage at the second locus within the stratified groups is dependent on: IBD allele sharing at locus 2, overall sample size, and IBD allele sharing and sample size within the strata.

In the examples given, the IBD status is known unequivocally for each observation. In analysis of data there will be observations for which only identity-by-state (IBS) status will be known. The proportion of observations for which only IBS status is known is dependent upon the informativeness of a given marker. In the case where IBD status is not known for all observations, there will be a reduction in the power to detect linkage.

Results are reported for α levels of .01, .001, and .0001. The α value used to determine significance within a study depends upon the conditions of the study. If a candidate gene is being tested, an α level of .01 may be used to determine significance; otherwise a more stringent criterion of .0001 may be suitable (Ott 1999).

Simulation studies can aid in determining if there is sufficient power to detect linkage, given a certain sample size and proportion of IBD allele sharing. These studies

can also help to conclude whether or not stratification is beneficial.

For simulation studies, sample sizes will be known a priori, however, the proportion of IBD allele sharing will not be known. Risch (1990*b*) showed that there is a close relationship between risk ratios λ and IBD sharing probabilities for various relative pairs, where λ is defined as the recurrence risk for a given relative pair (i.e., siblings) divided by the population prevalence (Risch 1990*a*). Locus-specific λ can be obtained by using information on a relative specific λ and a hypothesized number of loci involved in disease etiology. Locus-specific IBD sharing probabilities can be estimated, based upon locus specific estimates of λ (Risch 1990*b*). Simulation studies can then be used to calculate for what range of IBD allele sharing will stratification potentially be beneficial if genetic heterogeneity is present. Information can also be obtained on how much power is sacrificed if the hypothesis of heterogeneity is incorrect and IBD allele sharing is homogeneous between strata. In addition, simulation studies can be done to determine under what conditions it would be beneficial to stratify based upon IBD status at one locus and test for linkage at a second locus. Here the amount of IBD allele sharing at the first locus and second locus would be known a priori. It could then be determined what amount of IBD allele sharing in the stratified groups would be necessary for stratification to be beneficial. The simulation studies, which are described, can be implemented using the computer program STRAT (Laboratory of Statistical Genetics, Rockefeller University). Although stratification can be advantageous, it should be done with caution to avoid a potential loss in power to detect linkage.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Laboratory of Statistical Genetics, Rockefeller University, http://linkage.rockefeller.edu (for the STRAT computer program [S.M.L.])

Online Mendelian Inheritance in Man (OMIM), http://www3.ncbi.nlm.nih.gov/Omim (for alcoholism [MIM 103780], bipolar disorder [MIM 125480], schizophrenia [MIM 181500], type I diabetes [MIM 222100], and type II diabetes [MIM 125853])

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